Kidney International (2008) **74**, 255–256. doi:10.1038/ki.2008.310

Intensity of renal support does not affect outcomes in critically ill patients with AKI

The delivery of renal-replacement therapy in critically ill patients with acute kidney injury (AKI) is controversial with regard to dialysis dose, dialysis method, and membrane used. The Veterans Administration/National Institutes of Health Acute Renal Failure Trial Network study examined two strategies for renal-replacement therapy. In the multicenter, prospective, randomized, parallel-group trial, eligible patients had AKI clinically consistent with acute tubular necrosis and requiring renal-replacement therapy, as well as sepsis or failure of one or more nonrenal organ systems. All subjects received intermittent hemodialysis when they were hemodynamically stable and continuous venovenous hemodiafiltration or sustained low-efficiency dialysis when they were hemodynamically unstable. Subjects received either the intensive-therapy or the less-intensive-therapy strategy. In the intensive-therapy strategy, dialysis was provided in one of the previously described modes six times per week. If continuous venous hemodiafiltration was provided, it had a flow rate of the total effluent of 35 ml/kg of body weight per hour. The less-intensive strategy provided dialysis three times per week or had a total-effluent flow rate of 20 ml/kg. The goal in both groups was to provide a single-pool Kt/V of between 1.2 and 1.4 per session.

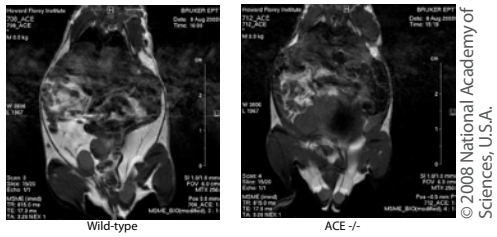
Outcomes were similar in the two groups. The primary study end point, death from any cause at day 60, occurred in 53.6% and 51.5% of the intensive-strategy and less-intensive-strategy groups, respectively ($P = 0.47$). No differences were seen between groups in the in-hospital death rate, the rate at which subjects were discharged to home off-dialysis, recovery of renal function by day 28, ICU-free days, or organ failure-free days.

The authors conclude that intensive renal support in critically ill patients with AKI does not decrease mortality, accelerate recovery of kidney function, or alter the rate of nonrenal organ failure. Prior works suggesting that a threshold for adequacy influences outcomes are not obviated by these results. (*N Engl J Med* advance online publication, 20 May 2008, doi:10.1056/NEJMoa0802639)

Lynda Szczech

Mice lacking angiotensin-converting enzyme have higher energy expenditure, less fat, better glucose clearance

In addition to its role in the storage of fat, adipose tissue acts as an endocrine organ and contains a functional renin–angiotensin system (RAS). Angiotensin-converting enzyme (ACE) plays a key role in the RAS by converting angiotensin I to the bioactive peptide angiotensin II. Jayasooriya *et al.* studied the effect of targeting the RAS in body energy homeostasis and glucose tolerance by comparing homozygous mice in which the gene for ACE had been deleted ($ACE^{-/-}$) with wild-type littermates. $ACE^{-/-}$ mice had lower body weight and a lower proportion of body fat, especially in the abdomen. Comparison of axial magnetic resonance images of $ACE^{-/-}$ and wild-type mice shows the influence of ACE deficiency on the accumulation of android fat, particularly in the visceral region (Figure). $ACE^{-/-}$ mice had greater fed-state total energy expenditure and resting energy expenditure than wild-type littermates. There were pronounced increases in gene expression of enzymes related to lipolysis and fatty acid oxidation (lipoprotein lipase, carnitine palmitoyl transferase, long-chain acetyl coenzyme A dehydrogenase) in the livers of $ACE^{-/-}$ mice and also lower plasma leptin. In contrast, no differences were detected in daily food intake, activity, fed-state plasma lipids, or proportion of fat excreted in fecal matter. In conclusion, the reduction in ACE activity is associated with a decreased accumulation of body fat, especially in abdominal fat depots. The decreased body fat in $ACE^{-/-}$ mice is independent of food intake and appears to be due to a high energy expenditure related to increased metabolism of fatty acids in the liver and glucose tolerance. (*Proc Natl Acad Sci USA* 2008; **105**: 6531–6536; doi:10.1073/pnas.0802690105)

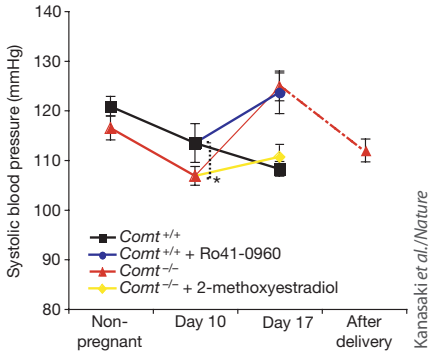


Proton density-weighted axial magnetic resonance images across the body of $ACE^{+/+}$ and $ACE^{-/-}$ mice. Bright, white areas denote fat.

Detlef Schlöndorff

Deficiency in catechol-O-methyltransferase and 2-methoxyestradiol is associated with preeclampsia

Preeclampsia is characterized by placental hypoxia, hypertension, proteinuria, and edema. Intensive investigations have not clarified the mechanisms that mediate appearance of this syndrome. Recent work has suggested that hypoxia-driven disruption of the angiogenic balance involving vascular endothelial growth factor (VEGF)/placenta-derived growth factor (PLGF) and soluble Fms-like tyrosine kinase-1 (sFLT-1, the soluble form of VEGF receptor 1) might contribute to some of the maternal symptoms of preeclampsia. However, preeclampsia does not develop in all women with high sFLT-1 or low PLGF levels, and it also occurs in some women with low sFLT-1 and high PLGF levels. Moreover,



Systolic blood pressure in nonpregnant mice and pregnant mice on days 10 and 17 of gestation and 10 days after delivery.

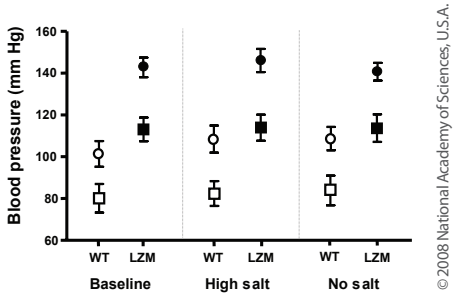
recent experiments strongly suggest that several factors affecting the vasculature are probably elevated because of placental hypoxia in preeclamptic women, indicating that an upstream molecular defect or defects may contribute to the condition. In a recent publication, Kanasaki *et al.* report that pregnant mice deficient in catechol-O-methyltransferase (COMT) showed a preeclampsia-like phenotype resulting from an absence of 2-methoxyestradiol, a natural metabolite of estradiol. The blood pressures of *Comt*$^{-/-}$ mice were significantly elevated late in pregnancy but returned to normal levels within 10 days after delivery, mimicking a similar trend observed in post-delivery preeclamptic women (Figure). Importantly, exogenous 2-methoxyestradiol prevented an increase in blood pressure in pregnant *Comt*$^{-/-}$ mice. Also, an inhibitor of COMT (Ro41-0960) administered to wild-type pregnant mice elevated blood pressure during later stages of pregnancy. Proteinuria, another clinical feature of preeclampsia, was higher in *Comt*$^{-/-}$ mice. Wild-type mice treated with the inhibitor of COMT also excreted more urinary albumin, and administration of 2-methoxyestradiol to pregnant *Comt*$^{-/-}$ mice prevented proteinuria. Electron microscopy revealed kidney glomerular endothelial cell detachment, swelling, and vacuolization late in pregnancy in *Comt*$^{-/-}$ mice; these glomerular lesions were not observed in pregnant 2-methoxyestradiol-treated *Comt*$^{-/-}$ mice. 2-Methoxyestradiol was generated by COMT in the placenta and increased in concentration during the third trimester of normal human pregnancy. The authors also found that the circulating levels of 2-methoxyestradiol were lower in female mice with preeclampsia than in normal pregnant female mice, and that COMT protein expression was significantly lower in the third-trimester preeclamptic placentae than in control placentae. Among several actions, 2-methoxyestradiol inhibits hypoxia-inducible factor-1α (HIF-1α), a transcription factor that senses tissue oxygen tension and regulates the expression of hypoxia-induced genes. Because HIF-1α is induced in placentae of preeclamptic women, it is likely that diminished COMT/2-methoxyestradiol levels may contribute to the elevation of placental HIF-1α. These studies suggest that 2-methoxyestradiol may have utility as a plasma and urine diagnostic marker for preeclampsia and could serve as a therapeutic agent. (*Nature* advance online publication, 11 May 2008, doi:10.1038/nature06951)

Juan Oliver

Hypertension resulting from a defect in vascular function

Genetic studies of patients with early-onset hypertension or hypotension inherited in the classic mendelian manner have identified abnormalities in renal sodium handling, suggesting that hypertension arises exclusively from impaired renal salt excretion and extracellular volume expansion. Acute changes in vascular tone can increase vascular resistance and blood pressure, but whether primary abnormalities of vascular smooth muscle tone can cause hypertension remains unclear. Increases in intracellular calcium in vascular smooth muscle cells activate myosin light chain kinase, which phosphorylates myosin light chains, activating myosin ATPase and increasing muscle cell contraction and vascular tone. Conversely, activation of myosin light chain phosphatase dephosphorylates myosin light chains and causes vascular smooth muscle relaxation. The relative proportion of phosphorylated and dephosphorylated myosin light chains thus determines the state of vascular tone. Nitric oxide, the most important endogenous vasodilator, causes smooth muscle cell relaxation by increasing cGMP and activating cGMP-dependent protein kinases (PKGI). Mice with deletion of the PKGI gene die shortly after birth, precluding detailed investigation of their cardiovascular function. This gene encodes two isoforms; one, PKGIα is expressed in vascular smooth muscle cells, where it binds and activates myosin light chain phosphatase, causing myosin light chain dephosphorylation and relaxation. Michael *et al.* now report the generation of knock-in mice harboring a discrete mutation in PKGIα, that disrupts the domain essential for PKGIα-mediated regulation of vascular smooth muscle myosin phosphatase. These LZM mice had sustained elevations of blood pressure that were independent of the salt intake (Figure). Importantly, glomerular filtration rate, renal plasma flow, and plasma aldosterone were no different between the control and LZM mice, making it unlikely that changes in renal function caused hypertension. Although subtle changes in extracellular fluid volume are notoriously difficult to detect, these experiments suggest that high blood pressure can arise from a primary abnormality of vascular smooth muscle function. This opens the door for new approaches to the diagnosis and therapy of a broad range of blood pressure disorders. (*Proc Natl Acad Sci USA* 2008; **105**: 6702–6707; doi:10.1073/pnas.0802128105)

Juan Oliver



Blood pressure in wild-type (WT) and LZM mice on normal-salt and altered-salt diets. LZM mice have significant increases in blood pressure compared with wild-type mice.